REMARKS

Claims 18-20, 23-27, 31-34, 37-43, 46-47 and 52 are pending in the application. No claims have been amended in this response and reconsideration is respectfully requested in light of the remarks below. Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim Rejection Under 35 U.S.C. § 103

Claims 18-20, 23-27, 31-34, 37-43, 46-47 and 52 stand rejected under 35 U.S.C. § 103 as being unpatentable over Dao *et al. (01/15/97, Blood, Vol. 89, pgs 446-456)* (hereinafter "*Dao*") and in view of Young *et al.* (09/01/1996, Blood, Vol. 88, pgs. 1619-1631) (hereinafter "*Young*"). Applicants respectfully traverse the rejection with respect to pending Claims 18-20, 23-27, 31-34, 37-43, 46-47 and 52. Reconsideration and withdrawal of the rejection is respectfully requested for the following reasons.

When rejecting claims under 35 U.S.C. §103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. See, e.g., *In re Bell* 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. Section 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art reference(s) must teach or suggest each and every limitation of the rejected claims; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their teachings; and (3) there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not in Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. §2142.

According to the Examiner, *Dao* teaches human $CD34^+$ progenitor cells transduced with retrovirus and cultured with FTL3 ligand (FL), to test whether FL might be able to replace the maintenance role provided by stromal support. The Examiner further contends that *Dao* teaches that the combination of firbronectin, to enhance gene transfer, and FL, to support progenitor survival, may ultimately replace the use of patient-derived stromal layers.

Applicants respectfully traverse. *Dao* fails to teach or suggest, *inter alia*, contacting a vector comprising a polynucleotide sequence encoding a heterologous gene with a population of $CD34^+Thy1^+Lin^-$ human pluripotent hematopoietic stem cells as required by independent Claims 18, 23,

37 and 52. This defect is not remedied by its combination with *Young*. While *Young* references a population of $CD34^+Thy1^+Lin^-$ cells and relates to stimulating the expansion of these cells using cytokines, the progeny were only tested for CD34 (*Young* at Table 2 at pg. 1627, and Fig. 5 at pg. 1629). Thus, neither *Dao* or *Young*, individually or in combination, teach or suggest, *inter alia*, contacting a vector comprising a polynucleotide sequence encoding a heterologous gene with a population of $CD34^+Thy1^+Lin^-$ human pluripotent hematopoietic stem cells as required by pending claims.

In addition, *Young* also states that "we made the novel observation that $CD34^+$ progeny can be produced from $CD34^+Thy^-1^+Lin^-$ cells in the presence of TPO." Accordingly, *Young* demonstrates that TPO acts on the $CD34^+Thy1^+Lin^-$ cells and supports differentiation of cells to mature MK morphology (*Young* at pg. 1828, columns 1-2), and in fact one third of the cells were $CD34^-$ at day 6 (page 1628, column 1, line 1 "two thirds of these cells expressed CD34"). Thus, rather than rendering obvious the instant invention, *Young* teaches away from the present invention.

Independent Claims 18 and 52 are directed in part to methods of obtaining genetically modified human pluripotent hematopoietic stem cells in the presence of a combination of mpl ligand, FLT3 ligand and firbronectin. Independent Claims 23 and 37 are directed in part to methods of obtaining human pluripotent hematopoietic stem cells in the presence of a combination of TPO, FLT3 ligand, IL-6 and fibronectin. *Doa* fails to teach or suggest this combination of molecules for obtaining genetically modified human pluripotent hematopoietic stem cells. Rather, *Dao* teach the use of FLT3 ligand in combination with IL-3, IL-6 and stem cell factor. *Dao* fails to teach or suggest the use of the FLT3 ligand in combination with mpl ligand and fibronectin as required by independent Claims 18 and 52. Likewise, *Dao* fails to teach or suggest the use of the FLT3 ligand in combination TPO, IL-6 and firbronectin as required by independent Claims 23 and 37.

The secondary reference, *Young*, does not cure the deficiencies of *Doa*. Rather, *Young* teaches the use of TPO alone, the combination TPO and IL-3, and the combination of TPO and C-kit ligand (KL). As *Young* states "to transduce hematopoietic stem cells with exogenous genes using retroviral vectors, there is a requirement to induce cycling of quiescent cells without inducing differentiation (*Young* at pg. 1630, first column, last paragraph). As noted above, however, *Young* demonstrates that TPO acts on the $CD34^+Thy1^+Lin^-$ and supports differentiation of cells to mature MK morphology. In view of this teaching, a person skilled in the art would not have transduced human hematopoietic progenitor cell in the presence of TPO. Thus, rather than rendering obvious the instance invention, *Young* again teaches away from the present invention.

In sum, none of the cited references, individually or in combination, teach or suggests the instant invention. Neither reference teaches or suggests use of the same cell population as the claimed methods. *Dao* and *Young* use a combination of molecules that are different from each other and from the claimed methods. The Examiner has merely picked a combination of molecules from *Dao* and *Young* to arrive at the Applicants' novel combination. Such hindsight perspective cannot support the asserted obviousness of the present invention.

Because *Dao* and *Young*, alone or in combination, fail to teach or suggest each and every limitation of the claimed invention, the Examiner has failed to establish a *prima facie* case, and the obviousness rejection should be withdrawn. Accordingly, the inventions recited in independent Claims 18, 23, 37, and 52 are unobvious over the disclosures of *Dao* and *Young*. Dependent Claims 19, 20, 24-27, 31-34, and 38-43, 46 and 47 are patentable for at least the same reasons. In view of the foregoing, Applicants respectfully request that the rejection of Claims 18-20, 23-27, 31-34, 37-43, 46-47 and 52 under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

Applicants respectfully submit that all pending claims of the captioned Application satisfy all requirements for patentability and are in condition for allowance. An early indication of the same is therefore respectfully requested.

If the Examiner determines that prosecution of the instant application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (415)-781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

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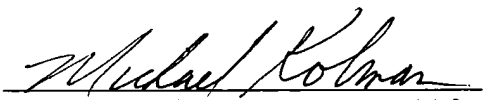
By: 
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